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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/735,014	12/12/2003	Audrey Goddard	10466/486	2599

7590 06/13/2006

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EXAMINER	
CHANDRA, GYAN	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 06/13/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/735,014	GODDARD ET AL.	
	Examiner	Art Unit	
	Gyan Chandra	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/8/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/22/2006 has been entered.

Status of Application, Amendments, And/Or Claims

Claims 22-26 are pending and are under examination.

Claim Rejections - 35 USC § 101 & 35 USC § 112

The rejection of claims 22-26 under 35 U.S.C. § 101 is maintained for the reasons of record as set forth in the office action mailed on 11/01/05.

The rejection of claims 22-26 under 35 U.S.C. 112, first paragraph, is maintained for the reasons of record as set forth in the office action mailed on 11/01/05.

The instant claims are drawn to an isolated antibody that binds to the polypeptide of SEQ ID NO: 83 and that the antibody is a monoclonal or humanized antibody. The claims also recite that the antibody is labeled.

Applicants argue that example 34, found on page 141 of the instant specification discloses that the PRO361 polypeptide tested positive in the Mixed Lymphocyte Reaction (MLR) Assay. Applicants list a number of patents including US Patent No. 5,648,376 and US Patent No. 5,817,306 that disclose use of MLR assay for identifying

molecules which supress an immune response. Applicants present references by Wolos et al. (1993), Fung Leung et al. (1995), Townsend et al (1996), Townsend et al. (1998), and Furukawa et al (1996) in support of their arguments. The applicant further states that in the light of teachings of Current Protocols in Immunology, one of skill in the art would understand that the disclosed assay on page 141 of the instant specification supports the claimed invention. Applicants argue that Dr. Fong's declaration supports that the polyepeptide of SEQ ID NO: 83 has a substantial utility because the polypeptide is inhibitory in the MLR assay.

Applicants' arguments have been fully considered but they are not persuasive because the mixed lymphocyte culture (MLC or also known as MLR) is a special case of antigen stimulation in which T lymphocytes respond to foreign histocompatibility antigen on unrelated lymphocytes or monocytes. Wolos et al used different inhibitory dosage of MDL-28, 842 in MLR assay to determine the IC 50 dose in generating cytotoxic T-cells. Townsend (1996) and (1998) teach using MLR assay for testing compounds along with known controls as cyclosporine (CsA) for their immunomodulatory effect. Similarly Furukawa (1996) and Fung-Leung (1995) also teach use of MLR assay to assess antigen specific CTL generation and IL-2 production. However, MLC is a functional assay of cellular response to stimulatory determinants associated predominantly with HLA class II molecules. The specification does not provide any data to support if the claimed PRO361 has statistically significant inhibition or activation against a control compound. The results of the assay are not predictive as Kahan clearly states that no *in vitro* immune assay predicts or correlates with *in vivo* immunosuppressive efficacy;

there is no surrogate immune parameter as a basis of immunosuppressive efficacy and/or for dose extrapolation from *in vitro* systems to *in vivo* conditions (Cur. Opin. Immunol. 4: 553-560, 1992; see entire document, particularly page 558, column 2). Piccotti et al. (Transplantation 67: 1453-1460, 1999) demonstrate that IL-12 enhances alloantigen-specific immune function as determined by MLC, but this result in vitro does not result in a measurable response *in vivo* (i.e. failure to accelerate allograft rejection) (see page 1459). Campo et al. (Biological Trace Element Res. 79: 15-22, 2001) demonstrate that while zinc suppresses alloreactivity in MLC, it does not decrease T-cell proliferation *in vitro* nor produce immunosuppressive effects *in vivo*. It is noted that the US Patent No. 5,817,306 and US Patent No. 5,648,376 disclose that the mixed lymphocyte response is valuable for identifying immune suppressive molecules in vitro that are useful in treating graft versus host diseases. Therefore, the MLR assay is art recognized.

However, difficulties arise in quantification when using MLC as a test for T cell function due to variations in stimulator cell antigens that determine the degree of genetic disparity between stimulator and responder cells. MLC is typically used for determining histocompatibilty in an individual and as a test for immunocompetence of T cells in patients with immunodeficiency disorders. When running the MLC assay for determining histocompatibility for transplantation, autologous controls combining self with irradiated self are necessary to normalize the response of each cell to stimulators. Furthermore, there is known inherent variability of individual cellular responses from day to day which requires performing the entire familial MLC at one time in the case of

determining histocompatibility for transplantation (page 246 in "Basic and Clinical Immunology"). When performing the MLC assay, each individual lot of a serum source should be screened for growth support capabilities and possible HLA antibodies (see page 1165 in "Manual of Clinical Laboratory Immunology"). Additionally, the screen should include a control response to a pool of allogeneic cells to measure maximum response and an autologous control to ensure low backgrounds.

The instant specification does not provide support for the asserted use of an antibody which binds the PRO361, based on the results of the MLR assay in Example 34 (page 141 of the specification). The specification at page 141, lines 33-35, states " any decreases below control is considered to be a positive result for an inhibitory compound, with decreases of less than or equal to 80% being preferred. However, any value less than control indicates an inhibitory effect for the test protein." The specification does not provide any values or data for the proteins tested in the assay. The specification does not provide any statistics for the values measured in the assay. The specification provides no information at all regarding the results of the assay except that the PRO363 is positive and that the statement that "any value any value less than control indicates an inhibitory effect for the test protein".

If the claimed invention is to be used for a therapeutic intervention of the immune response of an individual, the question to ask is how are the results of the MLR assay related to the asserted utility of the claimed invention? The previous Office actions go into great depth reguarding the nature of MLR assay and how those skilled in the art use this assay and what kind of determinations can be made about compounds which

are tested in this assay. The MLC or MLR assay is a measure of alloreactivity of one individual to another individual, rather than a general measure of immune function. This reactivity is governed by the antigenic disparity between the two individuals, which are being compared in the assay. Depending on the individuals being tested, the MLC may indicate stimulation if they are HLA-disparate or the MLC may indicate no stimulation if the individuals are HLA-identical. The ability of the claimed invention to inhibit proliferation in the MLC assay may not be a general inhibitory signal to lymphocyte proliferation, but rather a reaction to one of the MHC antigens on the responder cell. The instant specification fails to provide sufficient detail of the assay which was performed and fails to provide any data whatsoever in order for one of ordinary skill in the art to evaluate the conclusion that lymphocyte proliferation was stimulated by the claimed invention. As pointed out above, there are several controls which the art recognizes as being essential for meaningful results for this assay, including autologous controls, a control to determine maximum response, screening for possible HLA antibodies and growth support capabilities. Furthermore, there is known inherent variability of individual cellular responses from day to day, which would clearly dictate the need for internal controls. The specification indicates that CD4-IgG was used as a control, but it is not clear how this would control for background inhibition, stimulation or provide for a measure of maximal inhibition or stimulation. Lastly, the specification fails to provide any data or evidence of the results of the assay, therefore, one of ordinary skill in the art cannot evaluate the conclusion. The specification states "a PRO polypeptide is proliferation inhibitory in the MLR assay where the activity is observed as

80% or less of the controls", however, this does not indicate that statistical significance must occur for determination of a positive result in the assay. In conclusion, the results of the MLC or MLR assay do not support a specific and substantial utility for the claimed invention because one of ordinary skill in the art would not conclude that a molecule which tested positive in the assay of the specification wherein "any decreases below control is considered to be a positive result for an inhibitory compound" would be useful as a molecule in preventing suppression of immune response in an individual (asserted use). There is insufficient data presented, as well as insufficient controls used, to conclude anything regarding the ability to the encoded protein of the invention to be used in a substantial way to therapeutically inhibit an immune response, and further experimentation would be required to use the invention in this manner.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gyan Chandra whose telephone number is (571) 272-2922. The examiner can normally be reached on 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Gyan Chandra, Ph.D.
Art Unit 1646
06 June 2006
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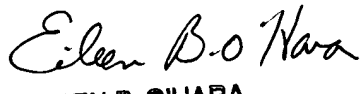

EILEEN B. O'HARA
PRIMARY EXAMINER